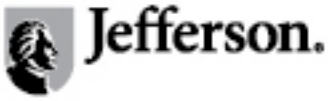

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Hyperosmolar therapy for raised intracranial pressure.

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durable control of recurrent respiratory papillomatosis.[4,5] Whether these pathways were also disrupted in the lung tumors of the patient described by Yuan and colleagues was not reported. Yuan et al. describe a cell-culture technique that was used to identify specific treatment for recurrent respiratory papillomatosis, but other agents may also be effective, and caution is advised before broadly using histone deacetylase inhibitors for recurrent respiratory papillomatosis.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Batra and Soo Hoo support our personalized cell technique that helped us to identify a therapy for progressive recurrent respiratory papillomatosis. Although we found that vorinostat was cytocidal in vitro and clinically effective in vivo, we agree with their comment that there may be additional therapeutic agents that our approach might be able to validate. Indeed, we are currently expanding our studies to explore such possibilities as well as applying our approach to nonviral neoplasia. However, we do not agree with their postulate that a "hit-and-run" mechanism was operative in the patient we described. Our polymerase-chain-reaction (PCR), reverse-transcriptase PCR, and cloning experiments indicate that wild-type and mutant HPV type 11 genomes were present in the laryngeal tumor and lung tumor, respectively. These findings are consistent with the well-documented role of HPV in virtually all cases of recurrent respiratory papillomatosis.[1-3]

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Since publication of their article, the authors report no further potential conflict of interest.

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Hyperosmolar Therapy for Raised Intracranial Pressure

TO THE EDITOR: Ropper (Aug. 23 issue)[1] recommends the use of mannitol at intervals of 2 to 4 or more hours to reduce intracranial pressure. Mannitol has been used for four decades to reduce intracranial pressure without solid evidence of benefit. In a randomized, controlled trial involving patients with intracerebral hemorrhage, mannitol improved neither the mortality nor the outcomes at 3 months.[2] Mannitol also did not improve cerebral blood flow as compared with saline in patients with intracerebral hemorrhage.[3] In a study involving 6 patients with large hemispheric infarctions, mannitol boluses were associated with a clinically significant reduction of brain volume, which was most marked in the normal hemisphere.[4] In another blinded study, mannitol administered in a 20% solution in boluses of 1.5 g per kilogram of body weight resulted in clinical improvement for 30 to 60 minutes in 5 of 12 patients with intracerebral hemorrhage, without a significant change in horizontal or vertical shift on magnetic resonance imaging.[5] Fre-

quent and large doses of mannitol result in formation of idiogenic osmoles, leading to a reduction in efficacy and even to rebound brain edema. We therefore think that mannitol should be used cautiously in patients with raised intracranial pressure.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Hypertonic saline has been associated with clinically significant renal insufficiency or acute renal failure in pediatric patients being treated for intracranial hypertension. In one study, 2 of 10 children being treated with mannitol and hypertonic saline for intracranial hypertension after traumatic brain injury required hemodialysis for renal failure.[1] In our study, we observed an increase in the serum creatinine level that was two to three times as high as the baseline level; this increase correlated with an increase in the serum sodium level above 160 mmol per liter (serum osmolarity, >320 mOsm per liter) with the use of hypertonic saline (without mannitol) in pediatric patients with intracranial hypertension and maintenance of a euvolemic hyperosmolar state.[2] As a result, our pediatric intensive care practitioners will attempt to avoid increasing the serum sodium level above 160 mmol per liter (serum osmolarity, >320 mOsm per liter) when administering hypertonic saline for treating intracranial hypertension in pediatric patients.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Ropper does not mention hyponatremic encephalopathy as a cause of raised intracranial pressure.[1] An equation for estimating the amount of hypertonic saline necessary to increase the serum sodium level is provided, and it is recommended that biochemical measurements (levels of serum sodium or serum osmolarity, blood urea nitrogen, and serum creatinine) be checked every 8 hours. It is not mentioned that conditions associated with raised intracranial pressure are frequently associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting.[2] Patients with SIADH and cerebral salt wasting can have hypertonic urine, with a combined urinary sodium and potassium concentration greater than that of plasma. The use of normal saline could actually result in a decrease in the serum sodium level, and the use of 3% saline could fail to raise the serum sodium level as much as calculated.[3] A continuous infusion of both normal saline and 3% saline will probably be required to maintain hyperosmolality, and the serum sodium level should be checked at least every 4 hours.[2] A new class of drugs, vasopressin antagonists, may have a role in achieving and maintaining hyperosmolality in patients with raised intracranial pressure.[4]

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Drs. Moritz and Ayus report serving as consultants to Otsuka Pharmaceuticals. No other potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1212351

TO THE EDITOR: Important details regarding mannitol were omitted from Ropper's article regarding management of elevated intracranial pressure. Ropper asserts that mannitol causes an osmotic diuresis, therefore increasing the serum sodium concentration, which leads to water shifting out of the brain due to an osmotic gradient. The article suggests that kidney function is necessary for mannitol to reduce intracranial pressure. However, in our practice, my colleagues and I have used mannitol (0.25 to 1.0 g per kilogram of body weight intravenously) to control intracranial pressure in patients with anuric renal failure who are receiving long-term intermittent hemodialysis. In this clinical situation, we have observed rapid, sustained decreases in intracranial pressure with the administration of mannitol. It is likely that the action of mannitol is due to increased plasma osmolarity after administration, causing water to shift out of the brain (for which renal function is not required).[1] Other possible mechanisms for the reduction of intracranial pressure associated with mannitol include an increase in cerebral perfusion,[2] causing cerebral vasoconstriction,[3] and decreased production of cerebrospinal fluid.[4] Other physicians may find, as we have, that the use of mannitol even in patients with chronic renal failure and elevated intracranial pressure is beneficial.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHOR REPLIES: Misra and colleagues eschew the use of mannitol for raised intracranial pressure. This view may have merit, but they cite their own randomized trial[1] that involved approximately 60 patients, a third of whom had a cerebral hemorrhage smaller than 20 ml in volume and a third of whom had a cerebral hemorrhage larger than 40 ml in volume. As I discuss in my editorial[2] on the article by Chesnut et al.[3] in this issue of the *Journal*, patients with small masses may not need treatment for intracranial pressure at all, and there may be a limited benefit to treating those with large lesions, so I am uncertain whether Misra's study settles the question of the usefulness of mannitol. If Misra and colleagues are questioning entirely the need to reduce intracranial pressure in cerebral hemorrhage, that is an interesting but separate polemic.

The risks of excessive dehydration in children are well noted by Huh and colleagues, and I commented in my article that serum sodium levels over 160 mmol per liter, arbitrarily stated by others to be the upper limit for safety, have been safely exceeded in adults.

Hyponatremic encephalopathy is an interesting entity, but in my experience it has not been obligatorily tied to brain swelling, especially when the cause is the natriuretic Nelson's syndrome. The other points made by Moritz and Ayus are worth noting, and vasopressin antagonists that cause hyperosmolarity are a new prospect as treatment for raised intracranial pressure. An additional issue regarding the correction of hyponatremia is the risk of "osmotic demyelination" (formerly called "central pontine myelinolysis") if the level of sodium is made to rise too rapidly.

In response to the point made by Benardete about mannitol being effective even in patients with renal failure: my article indicates that a "sustained" reduction of intracranial pressure requires osmotic diuresis. I accept that the continued circulation of mannitol in patients with renal failure might allow a prolonged hyperosmolar effect until the sugar is metabolized, but repeat dosing would be required to sustain hyperosmolarity, and chronic renal failure of a degree that prevents an osmotic diuresis is not typical in circumstances of raised intracranial pressure. Benardete is probably aware that the other oftencited effects of mannitol on intracranial pres-

sure have been minor or transient in clinical studies.

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Since publication of his article, the author reports no further potential conflict of interest.

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DOI: 10.1056/NEJMc1212351

Missing Data in Clinical Trials

TO THE EDITOR: Little et al. (Oct. 4 issue)[1] mention limiting "the burden and inconvenience of data collection on the participants" as one of several ideas for limiting missing data in the conduct of clinical trials. Actually, this idea should be a design feature, and it is also important in limiting the burden on the investigator (a critical factor in successful data retrieval as well as patient accrual). Prominent trialists have long championed simple randomized trials for these and other reasons.[2] Simple, minimal data collection must be one of the most effective strategies for the prevention of missing data.

This concept is sometimes difficult to sell to investigators who may envision ancillary studies and additional publications ensuing from more data. However, quality trumps quantity, and perhaps this should be made clearer in criteria for academic promotion.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Little and colleagues correctly point out that missing data are often the result of study designs that mandate study discontinuation when treatment is discontinued.[1] Intention-to-treat inference based on randomization requires that patient data be collected regardless of treatment status. However, an issue requires further clarification. When following patients who are off treatment, and methods are used to address data that are missing at random, the goal is to recreate a result that would have been obtained if patients who discontinued treatment had been followed after discontinuing treatment. The use of patients who are receiving treatment to impute the results for those who have discontinued treatment would seem to be problematic. In addition, if the common practice of no longer considering data on patients after treatment discontinuation is not altered, methods to address missing data that are based on statistical models will have no similar patients from whom to model the missing data. How do the authors suggest that we deal with this conundrum?

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No potential conflict of interest relevant to this letter was reported.

1. Flyer P, Hirman J. Missing data in confirmatory clinical trials. J Biopharm Stat 2009;19:969-79.

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THE AUTHORS REPLY: We agree with Lewis that limiting the burden on participants and investigators is important in the design of a study. Excessive data collection not only creates more opportunities for missing data, but it can distract attention from the collection of critical data. That said, covariate data, auxiliary data, and secondary-outcome data can serve valuable purposes, including improving the ability to understand and model the missing data.

Hirman and Flyer raise the important issue of the appropriate intention-to-treat analysis when patients go off the treatment protocol. We see three broad options, the relative usefulness of